PRM250
PATHWAYS OF IMPLEMENTATION OF MULTI-CRITERIA DECISION ANALYSIS INTO ORPHAN DRUG APPROVAL PROCEDURE FOR DRUG SUPPLY PROGRAMS IN RUSSIAN FEDERATION
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BACKGROUND: While the orphan drug supply program is in progress, development of decision-making rules for approving orphan drug for supply program of Russian Federation becomes very actual. Real world data provides evidence, that routine approaches for approving such kind of drugs, e.i. pharmacoeconomic conclusions, are not applicable. Than the need in more appropriate approaches is existed. Multi-criteria decision analysis is one such approaches (MCDA). **OBJECTIVE:** To evaluate prospective of implementation of MCDA in health care system of Russian Federation and to develop road map of MCDA in Russia. **METHODS:** Literature review, cluster analysis, interviewing experts. **RESULTS:** The first step (qualitive) to implement MCDA is to test various MCDA methods to find out optimal one for Russian Federation: it is expected to select the most relevant criteria from the wide range of them. First of all, MCDA is considered to be the instrument to improve the quality of discussion and its transparency, to underline different point of view and unmet needs. On the second stage it may be possible to use quantity MCDA assessment as a rule to approve orphan drugs for drug supply programs. Local recommendations for MCDA in Russian Federation has been published. **CONCLUSION:** Implementation of MCDA as assisting instrument for orphan drug approving for drug supply programs is likely to be a valuable approach, that may improve the quality, transparency of decision-making process and to provide social equity for accepting decisions.

PRM251
PROPENSITY SCORE MATCHING AND SUBCLASSIFICATION WITH MULTI-LEVEL TREATMENTS
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There is extensive literature on methods, such as propensity scoring, for estimating the causal effects for two treatments using real world data. Much less work has been done for the more general setting with three or more treatments. Whereas the literature has suggested that these propensity-based methods do not naturally extend to the multi-level treatment case, we show, using the concept of weak unconfoundedness, that adjusting for or matching on a scalar function of the covariates removes biases associated with observed covariates. We focused on subclassification and matching approaches as these have found to be effective for two treatments and are among the most popular methods in that setting. We apply the proposed methods to an analysis of the effectiveness of treatments for fibromyalgia from a prospective observational study. We also carried out a simulation study to assess the performance of those new methods relative to such approaches like: pairwise propensity score matching; matching on the Mahalanobis distance of all covariates; matching on the set of propensity scores (with the number of scores equal to the number of distinct treatment levels minus one (Rassen, 2013)); weighting on the inverse of the binary treatment propensity scores (McCaffrey, 2013). The simulations suggest that the proposed methods are simple and viable options for comparing the effectiveness of three or more treatments. RASSEN et al.: Matching by propensity score in cohort studies with three treatment groups. Epidemiology 24, 401–9. MCCAFFREY et al.: A tutorial on propensity score estimation for multiple treatments using generalized boosted models. Stat. Med. 32,3388–414.

PRM252
GETTING TO REIMBURSEMENT FASTER: COMBINING RANDOMISED, PRAGMATIC, AND OBSERVATIONAL CLINICAL TRIAL DATA
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Reimbursement authorities often require pharmaceutical companies to provide them with more than just placebo-controlled data from RCTs. Instead, they typically seek data from a wider "real-world" setting, where the focus is on generating evidence of comparative effectiveness. The natural temptation for many pharmaceutical companies is to provide this evidence from separate, post-market approval studies. However, this approach can be expensive and undoubtedly leads to delays in reimbursement. We propose that both the additional costs of evidence gathering and the delays between regulatory and reimbursement approvals could be reduced by combining the main design elements of randomised, pragmatic, and prospective observational studies into a single, integrated Phase 3/4 study. This single study approach would typically begin with a standard RCT phase where, for example, an initial cohort of patients would be randomised to receive either the investigational therapy or placebo. Either in parallel with or following this phase, a second patient cohort would be randomised under pragmatic clinical trial conditions with the aim of comparing the investigational therapy with placebo and a limited number of active comparator treatments. Lastly, a third (observational) cohort would be enrolled and allocated to a wider range of therapies, as per clinical practice. Data from the RCT cohort would be used to obtain limited regulatory approval. Following this, data from the pragmatic cohort, once available, would then be formally combined using standard statistical techniques with data from the RCT cohort in order to obtain a wider regulatory approval and possibly some form of conditional reimbursement. The pragmatic and observational cohorts would then provide the comparative effectiveness data to allow for reimbursement across different patient groups. We outline the strengths and weaknesses of this approach, and discuss its operational considerations.

PRM253
AN EPIDEMIOLOGIC MODELING APPLICATION TO PHARMACOECONOMICS FOR IMPROVED HEALTH CARE PLANNING
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Epidemiologic and pharmacoeconomic models differ in terms of populations considered, mathematical techniques used, and questions addressed. A typical pharmacoeconomic model assesses chronic or acute conditions, uses Markov techniques, and considers a closed patient group receiving a defined therapy to assess incremental costs needed to achieve gains in quality adjusted life years. A typical epidemiologic model assesses vaccination or public health interventions for infectious disease using differential equations and considers open populations representing communities to estimate prevalence or numbers of disease cases averted. The manner of conducting sensitivity analyses also differs. In oncology, in which multiple lines of treatment are available, the epidemiologic approach has application to estimate the patient point prevalence or the number of patients who can start on a line of therapy over a certain time period, when this cannot be determined from clinical trials or registers (which usually focus on single lines of therapy or limited types of patients that are not representative of the overall patient population). The approach consists of conceptualizing an open population that incorporates incidence of the condition and the transition of patients through various lines of treatment until death, and uses systems of difference/differential equations. Parameterization is challenging if there are several prognostic factors to describe the patient population, multiple or complex treatment pathways, and a wide range of variability. Parameters are obtained from the published literature, analyses of database information, and/or surveys to experts in the field. Steady state solutions of the model equations estimate point and period prevalence. This approach is applicable to gastrointestinal stromal tumours and multiple myeloma. Resulting estimates are important for budget impact analysis and health care services planning by reducing uncertainty associated with identifying the patient numbers eligible for a given treatment. Epidemiologic modelling permits a framework to estimate disease prevalence that is little used in pharmacoeconomics.

PRM254
NON-INTERVENTIONAL RESEARCH ETHICAL REQUIREMENTS IN ENGLAND AND FRANCE: SHARED EXPERIENCE FROM A BINATIONAL RESEARCH PROJECT
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BACKGROUND: Ethical review for non-interventional research is progressively becoming part of research standards. This evolution ensures that participants in research are respectfully considered. In practice, information on ethical requirements for non-interventional research seems insufficient. Increasing and legitimate expectations from peer-reviewed journals regarding reviews by ethics committees sometimes challenge researchers. In this presentation, we share our experience of investigating ethical requirements for conducting a questionnaire-based research on physicians in France and England. **METHODS:** This investigation consisted of a documentary analysis, including official guidance documents on ethical requirements, communications with institutions and publications reviews. Documents were identified using an ad hoc search on official websites. Publications were identified on PubMed. **FINDINGS:** In England, the service of the National Research Ethics Service (NRES) serves as the ethics reviewer. It offers an informal preliminary review of the study protocol and estimates ethical risks associated with non-interventional research projects. Depending of the target population, the methods and the risk level associated with the research project, the NRES states whether a formal ethics application is necessary or not. In case of low risk projects the NRES supplies an email which can be used as a justification for peer-reviewed journals. In France, structures to support ethical reviews for non-interventional research are the result of an on-going reform. *Comités de Protection de la Personne*, or CPPs, fulfil the role of ethics reviewers although they were initially designed to collaborate for hospital-based research. Gaining ethical review in France was more complex due to the infrequent character of such request from the industry. **CONCLUSION:** This experience showed the increasing role of ethical requirements in non-interventional research. It is a domain in constant movement which calls for innovative approaches to compile and disseminate information regarding ethical requirements for non-interventional research across Europe and the world, especially regarding cross-national research projects.

PRM255
REAL WORLD STUDIES, CHALLENGES, NEEDS AND TRENDS FROM THE INDUSTRY
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OBJECTIVES: To understand key challenges, needs and trends for conducting real world studies (RWS). **METHODS:** An online survey conducted in September 2013 within key players in the pharmaceutical and medical device industry in EU and US. 456 persons have been solicited through emails and phone calls, 107 have responded to the questionnaire. Respondents were mostly occupying senior positions in medical affairs, health economics and outcome research. **RESULTS:** 27% RWS conducted are requested by Health Authorities, 73% on the industry initiative. 75% of those studies are subcontracted to a CRO. The main criteria of choice are the experience in RWS, particularly in the regulation process, the capacity to deliver on time and a flexible and adaptable structure. The RWS activity is expected to increase by 25 % in the next two years. Most of those studies have safety and effectiveness objectives and to a lesser extent drug utilization and health economics and the most common therapeutic areas are: oncology, cardiovascular and metabolic disorders. In addition, pharmaceutical companies are conducting more and more epidemiological studies to prepare dossiers for market access (disease understanding, unmet needs, population targeting). **CONCLUSION:** The pharmaceutical market is becoming global and is expanding into new countries and therapeutic areas. The result is an increase in the need for RWS where the regulatory agencies are asking for additional data

concerning the long term safety and effectiveness of the drugs when used on larger populations. Pharmaceutical companies face big challenges for the coming years especially in EU and there is an increase need for local regulatory knowledge. There's still need to increase awareness for the importance of real world studies and the impact it has on the patient's life.

PRM256

PUBLICATION MANUAL OF BUDGET IMPACT ANALYSIS (BIA) BY THE DEPARTMENT OF SCIENCE AND TECHNOLOGY OF THE MINISTRY OF HEALTH (DECIT)

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The epidemiological and economic methods applied to health technologies evaluations had a significant development in the last two decades. The need to balance the incorporation of new technologies in health care and limited financial resources promoted the construction and application of instruments supporting the decision making of health technology. The requirement Budget Impact Analysis formally stated in Law 12.401/2011 establishing the incorporation process technologies in SUS. In this context, in 2010/2011, the National Agency of Sanitary Surveillance (ANVISA) and DECIT, in partnership Institute for Health Technology Assessment (IATS) for drawing up of this guideline. In the first stage of development were used international recommendations of Canada, Australia, the UK and Poland, the recommendations of the International Society for PharmacoEconomics and Outcomes Research (ISPOR) and the methods used in studies of budgetary impact that had already been published. Afterwards, drafted a preliminary version of the Guideline and a standard tool - Excel worksheets - to estimate the uptake of monetary resources required for adoption of new technologies. Revisions were carried out by technicians DECIT and health agencies, and the proposal was submitted to the Working Group on Development of Methodology REBRATS, composed of experts and academic researchers from several Brazilian states. Were also carried out workshops for the application of spreadsheets. In 2012, the first edition of the Guidelines was published two thousand copies in Portuguese in order to provide best practice recommendations for studies of budget impact.

DISEASE - SPECIFIC STUDIES

RESPIRATORY-RELATED DISORDERS – Clinical Outcomes Studies

PRS1

PROSPECTIVE STUDY ON COST-EFFECTIVENESS OF NURSE INTERVIW INTRODUCING RETESTING WITH IN VITRO DIAGNOSTICS (IVD) TO PARENTS OF CHILDREN WITH SUSPECTED FOOD ALLERGY IN FINLAND

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OBJECTIVES: Accordance to Finnish Allergy Program 2008-2018, to decrease food avoidance diets by 50%. Focus in algorithm with patient history +IVD in school children with suspected food allergy and reason for declining re-diagnosis. NICE clinical guideline (Food Allergy Diagnoses, 2011) suggested further work made on effect of diagnosing allergies in realistic population and cost effectiveness of retesting. **METHODS:** Prospective trial with patients from Finnish primary care database (2885 school children). School kitchen had allergy restricted diets for 179 children. In the pilot phase, 179 families were contacted by letter. Of the 24 who were included in pilot, 17 were not allergic (70%). In this study families were interviewed by telephone. Of 156 families 107 agreed to participate in this study and 47 children will be diagnosed by component resolved diagnostics (CRD) and 60 with sIgE and CRD. **RESULTS:** Prevalence of food avoidance diets: 6,2%. Reasons for declining re-testing: 23 were not allergic, 9 were busy, 9 have own physician, 3 did not believe allergy tests, 8 scared of needles, 7 already tested, 4 tested often due to health problems, 2 in pilot study and 7 did not recognize a benefit. **CONCLUSIONS:** Telephone consultation by nurse decreased special diets for 23 children (13%) and 39 (22%) had non-medical reason to decline retesting. Nurse consultation to introduce retesting with IVD can be considered as cost effective approach in decreasing food avoidance diets in children.

PRS2

EFFECTIVENESS OF MONTELUKAST ON ASTHMA CONTROL IN INFANTS: A CLAIMS DATA STUDY

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OBJECTIVES: Montelukast 4mg (MTL-4) is an add-on therapy for asthmatic infants. Given the quality and exhaustivity of the data, French claims data (SNIIR-AM) is a relevant tool to investigate MTL-4 effectiveness in infants. The objective was to compare the effectiveness of MTL-4, associated or not with ICS, vs. ICS without MTL-4, on health outcomes of infants with mild to moderate uncontrolled asthma. **METHODS:** Infants (6-24 months) receiving ≥ 2 consecutive dispensing of respiratory drugs from 2010 to 2011, and presenting an initial exacerbation within 6 months of the first dispensing were preselected. Asthma-related outcomes included hospitalizations, dispensing of oral corticosteroids, addition of short-acting beta agonists to existing respiratory therapy, switch to a higher ICS dosage, or nebulized CS. The studied groups were infants receiving MTL-4 +/- ICS (MTL-4 group) and infants receiving ICS without MTL-4 (ICS group). The two groups were matched, e. g. on initial therapy before initial exacerbation and past asthma related hospitalization. The two groups were compared, as to the occurrence of a new exacerbation and the total number of exacerbations during the 6 month follow-up following initial exacerbation. We also compared health care utilization between both groups. **RESULTS:** Among 115,489 infants (mean age: 13.9 months; 62.9% boys), 4,477 infants of the MTL-4 group were matched with 13,386 infants of the ICS group. In multivariate analysis, the risk of a new exacerbation was lower in infants of MTL-4 group compared to infants in ICS group (HR=0.91, IC95% [0.87; 0.95]). The total number of exacerbations did not differ between the 2 groups during the 6-month follow-up (p=0,8617), neither the cost of asthma management (344€ for MTL-4 group vs. 308€ for ICS group, p=0.1410). **CONCLUSIONS:** MTL-4 and ICS appear to be comparable therapeutic strategies, with similar effects on exacerbation and equivalent costs. The SNIIR-AM allows conducting comparative effectiveness research.

PRS3

CLINICAL TRIAL-BASED COST-EFFECTIVENESS ANALYSIS OF INDACATEROL (ONBREZ® 150 MCG) VERSUS TIOTROPIUM (SPIRIVA®) IN THE TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) IN TURKEY

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OBJECTIVES: COPD is a disease that is characterized by chronic and progressive restriction of the airflow. The cost of COPD medications can be reduced significantly by implementing a treatment algorithm that is consistent with the GOLD guidelines. Indacaterol and tiotrpium administered by inhalation are indicated for maintenance treatment of COPD in Turkey. We aimed to compare, from the perspective of the Turkish social security institution, the cost-effectiveness of indacaterol 150 mcg once daily and long-acting tiotropium 18 mcg once daily at months 3 and 6 in patients with moderate to severe COPD aged 30 years and above. **METHODS:** From payer perspective, a cost-effectiveness analysis based on two separate clinical trials (INTENSITY-once daily indacaterol and tiotropium vs. placebo and INHANCE-indacaterol vs tiotropium) was performed. The primary endpoints of the clinical trials (Trough FEV_1, Transition Dyspnea Index [TDI] and Saint Georges Respiratory Questionnaire [SGRQ]) were included in the cost-effectiveness analysis. Incremental cost effectiveness ratio (ICER) of indacaterol vs. tiotropium for different treatment success criteria (week 12 FEV_1 >0.12L increase, ≥1 improvement in TDI score, ≥4 decrease in SGRQ score) were compared. Incremental cost effectiveness ratios were calculated over incremental differences versus placebo. Probabilistic sensitivity analysis was performed using the Bootstrap method. **RESULTS:** FEV_1success rates at month 3 for indacaterol and ipratropium were 26.5% and 24.3%, respectively. At month 3, ICERs of indacaterol versus ipratropium were -1002TL for FEV_1, -434TL for TDI and -878TL for SGRQ. At month 6, FEV_1 success rates were 54.8 and 47.4%, TDI success rates were 58.7% and 54.4% and SGRQ success rates were 81.8% and 77.1%, respectively. ICERs of indacaterol versus ipratropium at month 6 were -616TL for FEV_1, -1049TL for TDI and -1014TL for SGRQ **CONCLUSIONS:** Based on this clinical trial-based analysis, indacaterol was cost effective treatment and cost reducing choice vs. tiotroprium in COPD treatment.

PRS4

A NETWORK META-ANALYSIS COMPARING THE EFFICACY AND SAFETY OF CEFTOBIPROLE AND SELECTED COMPARATORS IN THE TREATMENT OF HOSPITAL-ACQUIRED PNEUMONIA

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OBJECTIVES: Hospital-acquired pneumonia (HAP) is a severe respiratory tract infection which develops more than 48h after hospital admission. Ceftobiprole, the active moiety of its prodrug ceftobiprole medocaril, is a new cephalosporin with bactericidal activity against a broad spectrum of pathogens including resistant bacteria such as methicillin-resistant *S. aureus* (MRSA), penicillin-resistant *pneumococci* and*P. aeruginosa*. Ceftobiprole was shown safe and effective for the treatment of HAP (excluding ventilator-associated pneumonia), when compared with linezolid plus ceftazidime in a large-scale phase-III clinical trial (NCT00210964). **METHODS:** MEDLINE, EMBASE, Medline-In-Process and the Cochrane Library were searched for randomised controlled trials that included ceftobiprole and/or comparators ceftazidime, meropenem, imipenem/cilastatin, piperacillin/tazobactam, ciprofloxacin, levofloxacin, moxifloxacin and gentamicin as intervention in the treatment of HAP. The efficacy of ceftobiprole was compared to comparators using a random effects model implemented within a fully Bayesian framework. Primary outcome was clinical response after end of treatment in the clinically evaluable (CE) population. **RESULTS:** Eleven studies (2413 patients) with HAP were included in the analysis, 1618 patients were eligible for analysis of clinical response in the CE population. The comparative efficacies (odds ratio, 95% credible intervals) of ceftobiprole to each comparator were 0.92,0. 092-8.8 (ceftazidime), 1.1, 0.054-19 (piperacillin/tazobactam), 1.9, 0.12-30 (meropenem), 0.83, 0.019-32 (levofloxacin), 0.96, 0.047-16 (imipenem/cilastatin), and 0.87, 0.025-22 (ciprofloxacin). No comparison was possible to gentamicin or moxifloxacin due to a lack of comparative studies against other comparators. No significant difference was seen between ceftobiprole and any comparator in clinical response or in any of the secondary outcomes, including mortality and adverse events **CONCLUSIONS:** The results of this multi-treatment comparison support the comparable efficacy and safety of ceftobiprole to relevant comparators in the treatment of HAP. This analysis was limited by the small number of available studies, and by the fact that among the drugs compared, only ceftobiprole provides coverage of MRSA.

PRS5

COMPARATIVE EFFICACY OF UMECLIDINIUM BROMIDE VERSUS OTHER LONG-ACTING ANTICHOLINERGIC MONOTHERAPIES AS TREATMENTS FOR COPD PATIENTS

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